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(54) Title: USE OF VITAMIN D GLYCOSIDES FOR THE TREATMENT OR PREVENTION OF OSTEOPOROSIS

(57) Abstract

The present invention relates to methods for the treatment or prevention of osteoporosis by the administration of a vitamin D glycoside or vitamin D orthoester glycoside, or an analog thereof.

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Title of the Invention

USE OF VITAMIN D GLYCOSIDES FOR THE TREATMENT OR PREVENTION OF OSTEOPOROSIS

Field of the Invention

The invention is in the field of Medical Chemistry.

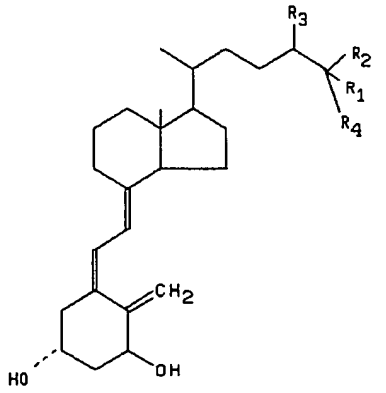
Background of the Invention

It is well known that females at the time of menopause suffer a marked loss of bone mass giving rise ultimately to osteopenia, which in turn gives rise to spontaneous crush fractures of the vertebrae and fractures of the long bones. This disease is generally known as postmenopausal osteoporosis and presents a major medical problem, both in the United States and most other countries where the life-span of females reaches ages of at least 60 and 70 years. Generally the disease, which is often accompanied by bone pain and decreased physical activity, is diagnosed by one or two vertebral crush fractures with X-ray evidence of diminished bone mass. It is known that this disease is accompanied by diminished ability to absorb calcium, decreased levels of sex hormones, especially estrogen and androgens, and a negative calcium balance.

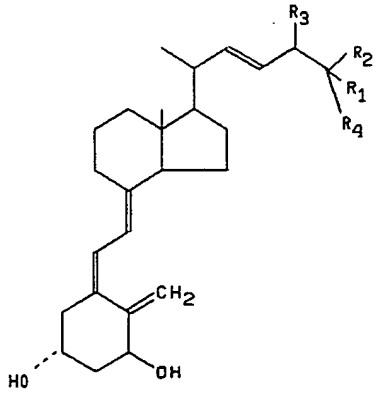
Methods for treating the disease have varied considerably but to date no really satisfactory treatment is yet known. For example, calcium supplementation by itself has not been successful in preventing or curing the disease and the use of sex hormones, especially estrogen, which has been reported to be effective in preventing the rapid loss of bone mass experienced in postmenopausal women, has been complicated by the fear of its possible carcinogenicity. Other treatments, for which variable results have again been reported, have included a combination of vitamin D in large doses, calcium and fluoride. The primary problem with this approach is that fluoride induces

structurally unsound bone, called woven bone, and in addition, produces a number of side effects such as increased incidence of fractures and gastrointestinal reaction to the large amounts of fluoride administered.

U.S. Patent No. 4,725,596 discloses methods for treating or preventing metabolic bone disease characterized by the loss of bone mass by administering at least one compound having the formulae (I) and (II):



(I)



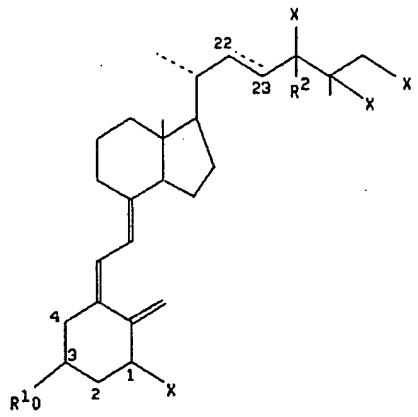
(II)

where R_1, R_2 and R_3 are each selected from the group consisting of hydrogen, hydroxyl, lower alkyl, acyl and O-alkyl and R_3 is selected from the group consisting of hydrogen, hydroxyl, keto, lower alkyl, acyl and O-alkyl.

See also, Tilyard, M.W. *et al., N. Eng. J. Med. 326*:357-362 (1992) and Caniggia. A., *et al., Metabolism 39*:43-49 (1990), who disclose the

treatment of osteoporosis with calcitriol (1α,25-dihydroxyvitamin D_3). However, this method has the significant disadvantage that high levels of these compounds, e.g., 1α,25-dihydroxyvitamin D_3, causes an increase of the blood calcium level above the normal range and concomitant toxicity.

U.S. Patent No. 4,410,515 discloses the following compounds having Formula (III) which are active in maintaining calcium and phosphorus metabolism and are useful for treating hypocalcemia in animals:

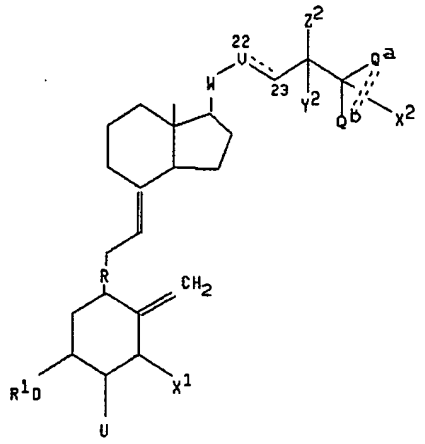


(III)

wherein the double bond between positions C-22 and C-23 is single or double; R^2 is hydrogen, CH_3 or CH_2CH_3; X is selected from the group consisting of hydrogen and $-OR^1$, where R^1 is hydrogen or a straight or branched chain glycosidic residue containing 1-20 glycosidic units per residue; with the proviso that at least one of the R^1 is glycosidic residue.

Summary of the Invention

The present invention relates to a method for treating or preventing osteoporosis in an animal having osteoporosis or susceptible to osteoporosis, comprising administering to the animal an effective amount of a compound having the formula:



wherein the bond between C-22 and C-23 is a single or a double bond;

Y^2 is hydrogen, fluorine, methyl, ethyl or OR^1;

Z^2 is F, H or X^2;

U is hydrogen, -OH or -O-(C_2-C_4 alkyl)-OH;

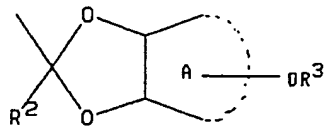
Q^a is CF_3 or CH_2X^2;

Q^b is CF_3 or CH_3;

R is a double bond or an epoxy group;

X^1 and X^2 are selected from the group consisting of hydrogen and OR^1;

R^1 is hydrogen or a straight or branched chain glycosidic residue containing 1-20 glycosidic units per residue, or R^1 is an orthoester glycoside moiety of the formula:



wherein A represents a glycofuranosyl or glycopyranosyl ring;

R^2 is hydrogen, lower alkyl (C_1-C_4), aralkyl (C_7-C_{10}), or aryl, with the proviso that aryl is phenyl or phenyl substituted by chloro, fluoro, bromo, iodo, lower C_1-C_4 alkyl, C_1-C_4 alkoxy; or naphthyl;

R^3 is hydrogen or a straight or branched chain glycosidic residue containing 1-20 glycosidic units per residue;

W is $CH\text{-}CH_3$ or O; and

V is CH_2 or O;

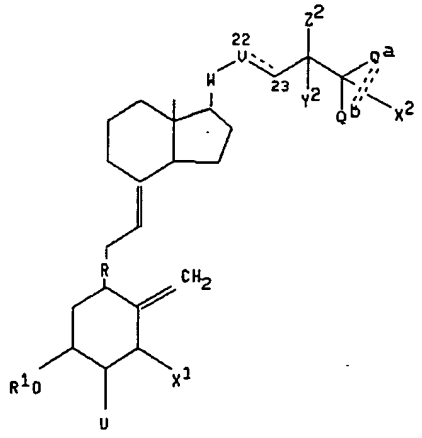
with the proviso that both W and V are not both O; and

"===" is either a single bond between Q^a and Q^b or a hydrogen atom on Q^a and Q^b, with the proviso that wherein "===" is a single bond, then X^2 is H; and

with the further proviso that at least one of the R^1 is either a glycosidic residue or an orthoester glycoside moiety.

Description of the Preferred Embodiments

The invention is related to the discovery that compounds having Formula (IV) are useful in treating and preventing osteoporosis:



(IV)

wherein the bond between C-22 and C-23 is a single or double bond;

Y^2 is hydrogen, fluorine, methyl, ethyl or OR^1;

Z^2 is F, H or X^2;

U is hydrogen, -OH or -O-(C_2-C_4 alkyl)-OH;

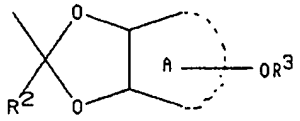
Q^a is CF_3 or CH_2X^2;

Q^b is CF_3 or CH_3;

R is a double bond or an epoxy group;

X^1 and X^2 are selected from the group consisting of hydrogen, and OR^1,

R^1 is hydrogen or a straight or branched chain glycosidic residue containing 1-20 glycosidic units per residue, or R^1 is an orthoester glycoside moiety of the Formula (V):



(V)

wherein A represents a glycofuranosyl or glycopyranosyl ring;

R^2 is hydrogen, lower alkyl, aralkyl, or aryl, with the proviso that aryl is phenyl or phenyl substituted by chloro, fluoro, bromo, iodo, lower C_1-C_4 alkyl, C_1-C_4 alkoxy; or naphthyl; and

R^3 is hydrogen or a straight or branched chain glycosidic residue containing 1-20 glycosidic units per residue,

with the proviso that at least one of the R^1 is either a glycosidic residue or an orthoester glycoside moiety;

W is $CH\text{-}CH_3$ or O; and

V is CH_2 or O;

with the proviso that both W and V are not both O; and

"===" is either a single bond between Q^a and Q^b or a hydrogen atom on Q^a and Q^b, with the proviso that wherein "===" is a single bond, then X^2 is H.

Any animal which experiences osteoporosis and which may benefit from the vitamin D glycosides and orthoester glycosides of Formula IV may be treated according to the present invention. Preferred animals are of course humans, in particular, pre- or post menopausal women. When administered

to a pre-menopausal woman, it is possible to prevent osteoporosis. When administered to a post-menopausal woman, it is possible to reverse the adverse consequences of osteoporosis mentioned above, and arrest the further deterioration of the bones.

The vitamin D glycosides and orthoester glycosides of the present invention have the distinct advantage that they promote calcium absorption through the intestine without effecting calcium mobilization from the bones. Thus, unlike 1,25-dihydroxyvitamin D_3 which effects calcium mobilization from the bones, the vitamin D glycosides and orthoester glycosides of Formula IV are uniquely suited for the treatment of osteoporosis.

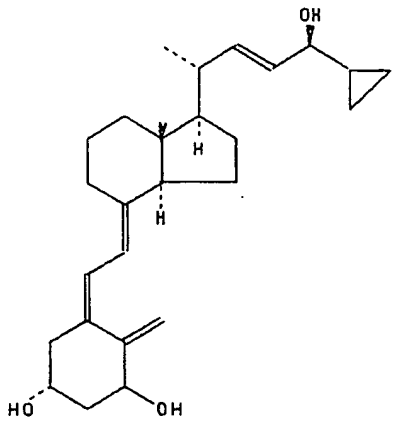
By glycosidic units are meant glycopyranosyl or glycofuranosyl, as well as their amino sugar derivatives. The residues may be homopolymers, random or alternating or block copolymers thereof. The glycosidic units have free hydroxy groups, or hydroxy groups acylated with a group R^4-(C=O)-, wherein R^4 is hydrogen, lower C_{1-6} alkyl, C_{6-10} substituted or unsubstituted aryl or C_{7-16} aralkyl. Preferably, R^4 is acetyl or propionyl; phenyl, nitrophenyl, halophenyl, lower alkyl substituted phenyl, lower alkoxy substituted phenyl, and the like or benzyl, lower alkoxy substituted benzyl and the like.

When the compounds of Formula (IV) have a double bond at position C-22 and a methyl group at C-24, they are derivatives of vitamin D_2, whereas if the bond at that position is single, and there is a lack of C_{24} alkyl, they are derivatives of vitamin D_3.

The compounds useful in the practice of the invention contain at least one glycoside residue at positions 1, 3, 24, 25 or 26. They may contain, however, more than one and up to five glycoside residues simultaneously.

Preferred are those glycosides derived from vitamins D_3 or D_2; 1-hydroxyvitamins D_3 or D_2; 1,24-dihydroxyvitamins D_2 and D_3; 1,25-dihydroxyvitamins D_3 and D_2; 24,25-dihydroxyvitamins D_3 or D_2; 25,26-hydroxyvitamins D_3 or D_2; 1,24,25-trihydroxyvitamins D_3 or D_2; and 1,25,26-trihydroxyvitamins D_3 or D_2. Among the most preferred are the glycosides of 1-hydroxyvitamins D_3 or D_2; and 1,25-dihydroxyvitamins D_3 or D_2,

1,24-dihydroxyvitamin D_3, 5,6-epoxy derivatives of vitamin D and its metabolites, 2-ß-(3-hydroxypropoxy)-1 alpha,25-dihydroxyvitamin D_3, as well as the side chain fluoro derivatives of 1,25-$(OH)_2$ vitamin D and 1-(OH) vitamin D. Also preferred are 20- and 22-oxa vitamin D derivatives including 20-oxa-1α(OH)D, 20-oxa-1α,25$(OH)_2D_3$, 22-oxa-1α(OH)D_3 and 22-oxa-1α,25(OH)D_3 as well as pseudo-1-alpha-hydroxyvitamin D derivatives such as dihydrotachysterol and 5,6-trans vitamin D_3 and their 25-hydroxy derivatives. Also preferred is calcipotriol having the formula:



See Krayballe, K., *Arch. Dermatol. 125*:1647 (1989).

The most preferred glycosides include vitamin D_3, 3β-(β-D-glucopyranoside); vitamin D_3, 3β-(β-D-fructofuranoside); vitamin D_3, 3β-(galactosyl); vitamin D_3, 3β-(β-maltoside); vitamin D_3, 3β-(β-lactoside); vitamin D_3, 3β-(β-trehaloside); vitamin D_3, 3β-raffinoside; vitamin D_3, 3β-gentiobioside; 1α-hydroxyvitamin D_3, 3β-(β-D-glucopyranoside); 1α-hydroxyvitamin D_3, 3β-(β-D-fructofuranoside); 1α-hydroxyvitamin D_3, 3β-(β-cellobioside); 1α-hydroxy-3β-(β-maltosyl)vitamin D_3; 1α-hydroxy-3β-raffinosylvitamin D_3; 1α-hydroxy-3β-gentiobiosylvitamin D_3; 1α-(β-D-glucopyranosyl)vitamin D_3; 1α-(β-D-fructofuranosyl)vitamin D_3; 1α-(β-galactosyl)vitamin D_3; 1α-(β-maltosyl)-vitamin D_3; 1α-(β-lactosyl)vitamin D_3; 1α-(β-trehalosyl)vitamin D_3; 1α-raffinosylvitamin D_3; 1α-gentiobiosylvitamin D_3; 1α, 25-dihydroxyvitamin D_3, 3β-(β-D-fructofuranoside); 1α, 25-

dihydroxyvitaminD$_3$,3β-(β-D-glucopyranoside);1α-(β-D-glycopyranosyl)-25-hydroxyvitamin D$_3$; 1α-(β-D-fructofuranosyl)-25-hydroxyvitamin D$_3$; 1α-hydroxy-25(β-D-fructofuranosyl)-vitamin D$_3$; 1α-hydroxy, 25-(β-glucopyranosyl)vitamin D$_3$; 1α-hydroxy, 25-(β-maltosyl)vitamin D$_3$; 1α-hydroxy, 25-(β-lactosyl)vitamin D$_3$; 1α-hydroxy, 25-β-trehalosylvitamin D$_3$; 1α-hydroxy,25-raffinosylvitaminD$_3$;and1α-hydroxy,25-gentiobiosylvitamin D$_3$. Also included are 1α,24-dihydroxyvitamin D$_3$, 3β-(β-D-glucopyranoside); 1α,24-dihydroxyvitamin D$_3$, 3β-(β-D-fructofuranoside); 1α-(β-D-glycopyranosyl)-24-hydroxyvitamin D$_3$; 1α-(β-D-fructofuranosyl)-24-hydroxyvitamin D$_3$; 1α-hydroxy-24(β-D-fructofuranosyl) vitamin D$_3$; 1α-hydroxy-24-(β-glycopryanosyl)vitamin D$_3$; 1α-hydroxy, 24-(β-maltosyl)vitamin D$_3$; 1α-hydroxy, 24-(β-lactosyl)vitamin D$_3$; 1α-hydroxy, 24-β-trehalosylvitaminD$_3$; 1α-hydroxy, 24-raffinosylvitaminD$_3$; and 1α-hydroxy, 24-gentiobiosylvitamin D$_3$.

In the case of multihydroxylated forms of the vitamins (e.g.: 1,25-dihydroxyvitamin D$_3$ has three hydroxy groups, at positions 1, 3 and 25), the preferred compounds of the invention are those wherein less than all of the multiple hydroxy groups are glycosylated, most preferably those were only one of the multiple hydroxy groups is glycosylated.

The glycosides can comprise up to 20 glycosidic units. Preferred, however, are those having less than 10, most preferred, those having 3 or less than 3 glycosidic units. Specific examples are those containing 1 or 2 glycosidic units in the glycoside residue.

The glycopyranose or glycofuranose rings or amino derivatives thereof may be fully or partially acylated or completely deacylated. The completely or partially acylated glycosides are useful as defined intermediates for the synthesis of the deacylated materials.

Among the possible glycopyranosyl structures are glucose, mannose, galactose, gulose, allose, altrose, idose, or talose. Among the furanosyl structures, the preferred ones are those derived from fructose, arabinose or xylose. Among preferred diglycosides are sucrose, cellobiose, maltose,

lactose, trehalose, gentiobiose, and melibiose. Among the triglycosides, the preferred ones may be raffinose or gentianose. Among the amino derivatives are N-acetyl-D-galactosamine, N-acetyl-D-glucosamine, N-acetyl-D-mannosamine, N-acetylneuraminic acid, D-glucosamine, lyxosylamine, D-galactosamine, and the like.

When more than one glycosidic unit is present on a single hydroxy group (i.e., di or polyglycosidic residues), the individual glycosidic rings may be bonded by 1-1, 1-2, 1-3, 1-4, 1-5 or 1-6 bonds, most preferably 1-2, 1-4 and 1-6. The linkages between individual glycosidic rings may be α or β.

The configuration of the oxygen linkage of a hydroxy group, or glycosidic residue attached to the vitamin D_3 or D_2 molecule may be either α (out of the plane of the paper) or β (into the plane of the paper). It is preferred if the configuration of the 3-hydroxy or glycosidoxy group at C-3 be β, and that, independently or simultaneously the configuration of the hydroxy or glycosidoxy at C-1 be α.

The starting vitamin D compounds are prepared or obtained according to methods which are well known to those of ordinary skill in the art. In particular, the 5,6-epoxy derivatives of vitamin D_3 are obtained as described in Jpn. Kokai Tokkyo Koho JP 58,216,178 [83,216,178], Dec. 15, 1983. The fluoro derivatives are made or obtained as described in Shiina, *et al., Arch. Biochem. Biophys. 220*:90 (1983). Methods for preparing the 20- and 22-oxa vitamin D derivatives are disclosed by Abe, J., *et al., Vitamin D Molecular, Cellular and Clinical Endocrinology*, p. 310-319, Walter de Gruyter & Co., Berlin (1988). U.S. Patent No. 4,719,205 to DeLuca *et al.* discloses methods for the preparation of 22,23-cis-unsaturated, 1-hydroxyvitamin D compounds. U.S. Patent No. 4,634,692 to Partridge *et al.* discloses methods for the preparation of 1,25-dihydroxy-24 (R or S)-fluorovitamin D. Japanese Patent Application, publication no. J55 111-460, discloses methods for the preparation of 24,24-difluoro-25-hydroxyvitamin D_3.

The water soluble glycosidic derivatives of the aforementioned compounds may be obtained according to Holick, U.S. Patent 4,410,515, the

contents of which are fully incorporated by reference herein. The vitamin D glycosyl orthoester compounds may be obtained according to U.S. Patent 4,521,410, the contents of which are fully incorporated by reference herein.

The compounds of the invention can be administered in any appropriate pharmaceutically acceptable carrier for oral, parenteral, or topical administration. They can be administered by any means that treats or prevents osteoporosis in animals, especially humans. The dosage administered will be dependent upon the age, health and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment and the nature of the effect desired. For example, systemic daily dosage of 1α-(β-glucopyranosyl)-25-hydroxyvitamin D_3 will be from about 0.001 micrograms/kg to 100 micrograms/kg preferably 0.01 to 1.0 micrograms per kg of body weight. Normally, from about 0.1 to 100 micrograms/kg per day of the glycoside or orthoester glycoside, in one or more dosages per day is effective to obtain the desired results. One of ordinary skill in the art can determine the optimal dosages and concentrations of other active vitamin D glycoside and orthoester glycoside compounds with only routine experimentation.

The compounds can be employed in dosage forms such as tablets, capsules, powder packets, or liquid solutions, suspensions or elixirs for oral administration, sterile liquid for formulations such as solutions or suspensions for parenteral use. Alternatively, the compounds may be administered transdermally via a patch or ointment and the like. The active ingredient will ordinarily be present in an amount of at least 10^{-6}% by weight based upon the total weight of the composition, and not more than 90% by weight. An inert pharmaceutically acceptable carrier is preferably used. Among such carriers include 95% ethanol, vegetable oils, propylene glycols, saline buffers, etc.

Having now generally described this invention, the same will be understood by reference to the following examples which are provided herein

for purposes of illustration only and are not intended to be limiting unless otherwise specified.

Example 1

Biologic Activity of 1,25-Dihydroxyvitamin D_3-3β-glucoside in Male Rats

A study in male rates was conducted to evaluate the potential biologic activity of 1α-(3β-glucopyranosyl),25-dihydroxyvitamin D_3 (1,25$(OH)_2D_3$-3β-glucoside). Male rats from Charles River were placed on rat chow for three days. They received by oral administration in 0.1 ml of propylene glycol one of the following compounds: 1,25$(OH)_2D_3$ (0.625 ηmol), 1,25$(OH)_2D_3$ (6.25 ηmol), 1,25$(OH)_2D_3$-3β-glucoside (6.25 ηmol). A control group received 0.1 ml of propylene glycol. The animals were dosed for five days. Twenty-four hour urine collections were made on Day 4 of the experiment, and on the fifth day, blood was collected for determination of serum calcium and 1,25$(OH)_2D_3$ concentrations. As can be seen in Table 1, 1,25$(OH)_2D_3$ increased the urinary calcium excretion and increased serum concentrations of calcium above the control values. 6.25 ηmol of 1,25$(OH)_2D_3$-3β-glucoside also increased the excretion of calcium in the urine but did not have a significant effect on the serum calcium concentration. Determination of serum concentrations of 1,25$(OH)_2D_3$ revealed that elevated levels of 1,25$(OH)_2D_3$ occurred in rats receiving 1,25$(OH)_2D_3$ at both doses as well as rats that received the 1,25$(OH)_2D_3$-3β-glucoside.

The increase in the excretion of urinary calcium is an indicator that both 1,25$(OH)_2D_3$ and 1,25$(OH)_2D_3$-3β-glucoside increase the efficiency of intestinal calcium absorption and mobilization of calcium from the bone. However, at the low and high dose of 1,25$(OH)_2D_3$, the undesirable effect on increasing the blood calcium above the normal range was observed. On the other hand, animals that received the highest dose of 1,25$(OH)_2D_3$-3β-

glucoside did not show an increase in the blood calcium above the normal range.

In osteoporosis, the blood calcium levels are normal. In order to effectively treat osteoporosis, it is necessary to provide $1,25(OH)_2D_3$ to stimulate the anabolic activity of bone cells. However, as shown above, $1,25(OH)_2D_3$ causes an undesired increase in blood calcium levels. Therefore, the vitamin D glycosides and orthoester glycosides are uniquely effective for the treatment of osteoporosis by increasing in a physiologic manner the efficiency of intestinal calcium absorption and bone calcium mobilization and increasing circulating concentrations of $1,25(OH)_2D_3$, without the side effects associated with the administration of $1,25(OH)_2D_3$.

Table 1

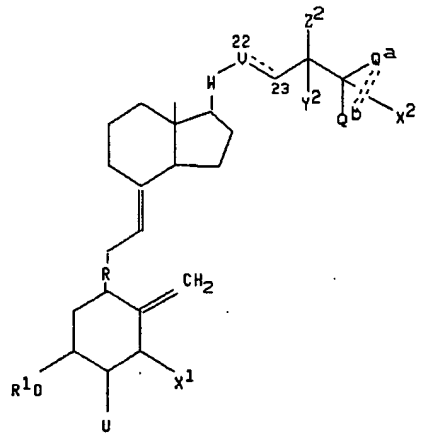
Evaluation of $1,25(OH)_2D_3$ and $1,25(OH)_2D_3$-3β-Glucoside in Male Rats

Compound	Dose (ηmoles)	24 Hour Urine Ca (mg/24h day 4)	Serum Ca (mg% day 5)	Serum $1,25(OH)_2D_3$ (pg/ml)
Vehicle	0	19	10.4	85
$1,25(OH)_2D_3$	0.625	43	11.4	356
$1,25(OH)_2D_3$	6.25	38	13	1409
$1,25(OH)_2D_3$-glc	6.25	40	10.6	358

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications if the invention to adapt it to various usages and conditions without undue experimentation. All patents and publications cited herein are incorporated by reference in their entirety.

What is Claimed is:

1. A method for treating or preventing osteoporosis in an individual having osteoporosis or susceptible to osteoporosis, comprising administering to said individual an effective amount of a compound having the formula:



wherein the bond between C-22 and C-23 is a single bond or a double bond;

Y^2 is hydrogen, fluorine, methyl, ethyl or OR^1;

Z^2 is F, H or X^2;

U is hydrogen, -OH or -O-(C_2-C_4 alkyl)-OH;

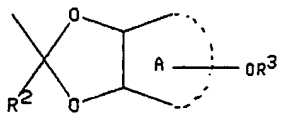
Q^a is CF_3 or CH_2X^2;

Q^b is CF_3 or CH_3;

R is a double bond or an epoxy group;

X^1 and X^2 are selected from the group consisting of hydrogen and OR^1;

R^1 is hydrogen or a straight or branched chain glycosidic residue containing 1-20 glycosidic units per residue, or R^1 is an orthoester glycoside moiety of the formula:



wherein A represents a glycofuranosyl or glycopyranosyl ring;

R^2 is hydrogen, lower alkyl (C_1-C_4), aralkyl (C_7-C_{10}); or aryl, with the proviso that aryl is phenyl or phenyl substituted by chloro, fluoro, bromo, iodo, lower C_1-C_4 alkyl, C_1-C_4 alkoxy; or naphthyl;

R^3 is hydrogen or a straight or branched chain glycosidic residue containing 1-20 glycosidic units per residue;

W is $CH\text{-}CH_3$ or O; and

V is CH_2 or O;

with the proviso that both W and V are not both O; and

"===" is either a single bond between Q^a and Q^b or a hydrogen atom on Q^a and Q^b, with the proviso that wherein "===" is a single bond, then X^2 is H; and

with the further proviso that at least one of the R^1 is either a glycosidic residue or an orthoester glycoside moiety.

2. The method of claim 1, wherein said compound is $1,25(OH)_2D_3$-3β-glucoside.

3. The method of claim 1, wherein said compound is administered in an amount ranging from about 0.1 to 100 micrograms/kg per day.

4. The method of claim 1, wherein said compound is administered as part of a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

5. The method of claim 1, wherein said individual is suffering from or has suffered from menopause.

6. The method of claim 1, wherein said compound is administered to a woman prior to the onset of menopause.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/12506

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) : A61K 7/42, 31/59, 31/70
US CL :514/35, 167, 171; 536/4.1, 17.2, 18.1, 53, 55.2; 568/665, 817, 819
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/35, 167, 171; 536/4.1, 17.2, 18.1, 53, 55.2; 568/665, 817, 819

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4,410,515 (HOLICK ET AL) 18 October 1983, see entire document.	1-6
A	US, A, 4,740,364 (HODGEN) 26 April 1988, see entire document.	1-6
A	US, A, 4,772,467 (PAK) 20 September 1988, see entire document.	1-6
A	US, A, 4,894,373 (YOUNG) 16 January 1990, see entire document.	1-6
A	US, A, 5,013,728 (GRODBERG) 07 May 1991, see entire document.	1-6

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
24 February 1994

Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/12506

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 5,104,864 (DE LUCA ET AL) 14 April 1992, see entire document.	1-6
A	US, A, 5,116,828 (MIURA ET AL) 26 May 1992, see entire document.	1-6
A	US, A, 5,167,953 (HOLICK ET AL) 01 December 1992, see entire document.	1-6
A,P	US, A, 5,194,248 (HOLICK) 16 March 1993, see entire document.	1-6
A	WO, A, 91/05537 (TRUSTEES OF BOSTON UNIVERSITY) 02 May 1991, see entire document.	1-6
Y	The Journal of Biological Chemistry, Volume 252, No. 8, issued 25 April 1977, Joseph L. Napoli et al, "Solanum glaucophyllum As Source of 1,25-Dihydroxyvitamin D(sub 3)", pages 2580-2583, especially page 2580.	1-6
Y	Burger's Medicinal Chemistry, 4th Edition, Part II, issued 1979, Joseph L. Napoli et al, "Blood Calcium Regulators", pages 725-739, especially pages 727-730.	1-6
Y	Chemical Abstracts, Volume 83, No. 18, issued 1975, Kazuo Shirai et al, "Stability of vitamin D(sub 2) tetraacetylglucoside. Ergocalciferyl-2,3,4,6-tetra-O-acetyl-D-glucoside", abstract 152290w, Vitamins, 49 (8), issued 1975, pages 339-344.	1-6
Y	Chemical Abstracts, Volume 84, No. 5, issued 1976, Kazuo Shirai et al, "Vitamin D glucuronosides", abstract 84:3137n, Japan Kokai 75,101,351, issued 11 August 1975.	1-6
A	The New England Journal of Medicine, Volume 326, No. 6, issued 06 February 1992, Murray W. Tilyard et al, "Treatment of Postmenopausal Osteoporosis With Calcitriol or Calcium", pages 357-362.	1-6
A	Arch Dermatol, Volume 125, issued December 1989, Knud Kragballe, "Treatment of Psoriasis by the Topical Application of the Novel Cholecalciferol Analogue Calcipotriol (MC 903)", pages 1647-1652.	1-6
A	Metabolism, Volume 39, No. 4, Suppl. 1, issued April 1990, A. Caniggia et al, "Long-Term Treatment With Calcitriol in Postmenopausal Osteoporosis", pages 43-49.	1-6